Measles
Meningitis
Diphtheria

Global Medicine Course

Brooks AFB, TX

5 February 2003, 15:30-16:30

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Measles: Basic Characteristics

- Also known as rubeola
- Acute viral illness
- Primarily affects children
- Highly contagious
- Paramyxovirus
  - RNA, single stranded
- Vaccine preventable
  - Potential to be eliminated

Measles: History

- Human disease since 3000-5000 BC
- Needs large population to propagate
  - Not feasible until Mesopotamia
- Middle East → Eastern Mediterranean → Roman Empire in 500 AD →
- Africa, India, China
- New World from Columbus

Measles: History

- Described in antiquity
  - Rhazes, Persian physician, 910 AD
  - Japanese treatise in 998 AD
  - China in 11th century AD
- Vaccine trials in 1960's
  - Early success, but smallpox received funds
- WHO focused on measles in 1990's
  - Current goal: decrease cases by 90% and mortality by 95%

Measles: Epidemiology

- 1990's: Present in all countries
  - 1995: 44 million cases
    - 1/3 of children born worldwide
    - 1.1 million deaths for children <5
- Currently: 1-2 million cases reported yearly
  - Thought to be gross underestimation
  - Most countries require reporting
- 800,000 deaths worldwide annually

Measles: Epidemiology

- Seasonal
  - Peaks in late winter or spring
  - Tropical countries: dry, cool season
  - Why?
    - Behavioral? Other infections predisposing?
- Males and females affected equally

Measles: Epidemiology

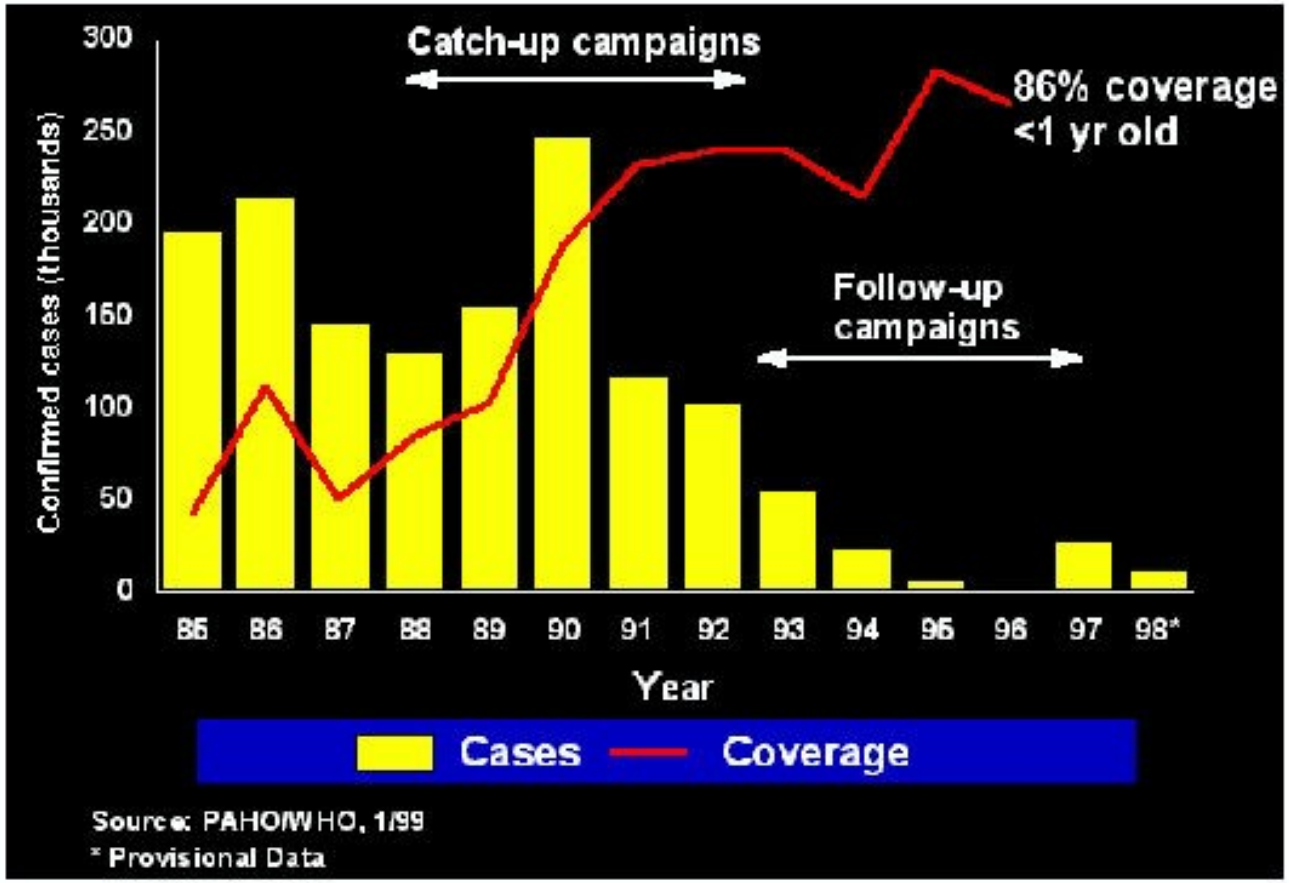
- Pre-Vaccine
  - Epidemics
  - Every 1-3 years
  - Age: 3-15 months
  - More frequent epidemics = younger age = urban > rural
  - Importation to remote, naïve population can be devastating
- Post-Vaccine
  - Small epidemics
  - Every 5-10 years
  - Age of onset = older
    - Adolescents, young adults with 1 vaccine
  - Majority of cases may be in vaccinated patients
  - Cause: accumulation of unvaccinated population

Measles: Geographic Distribution

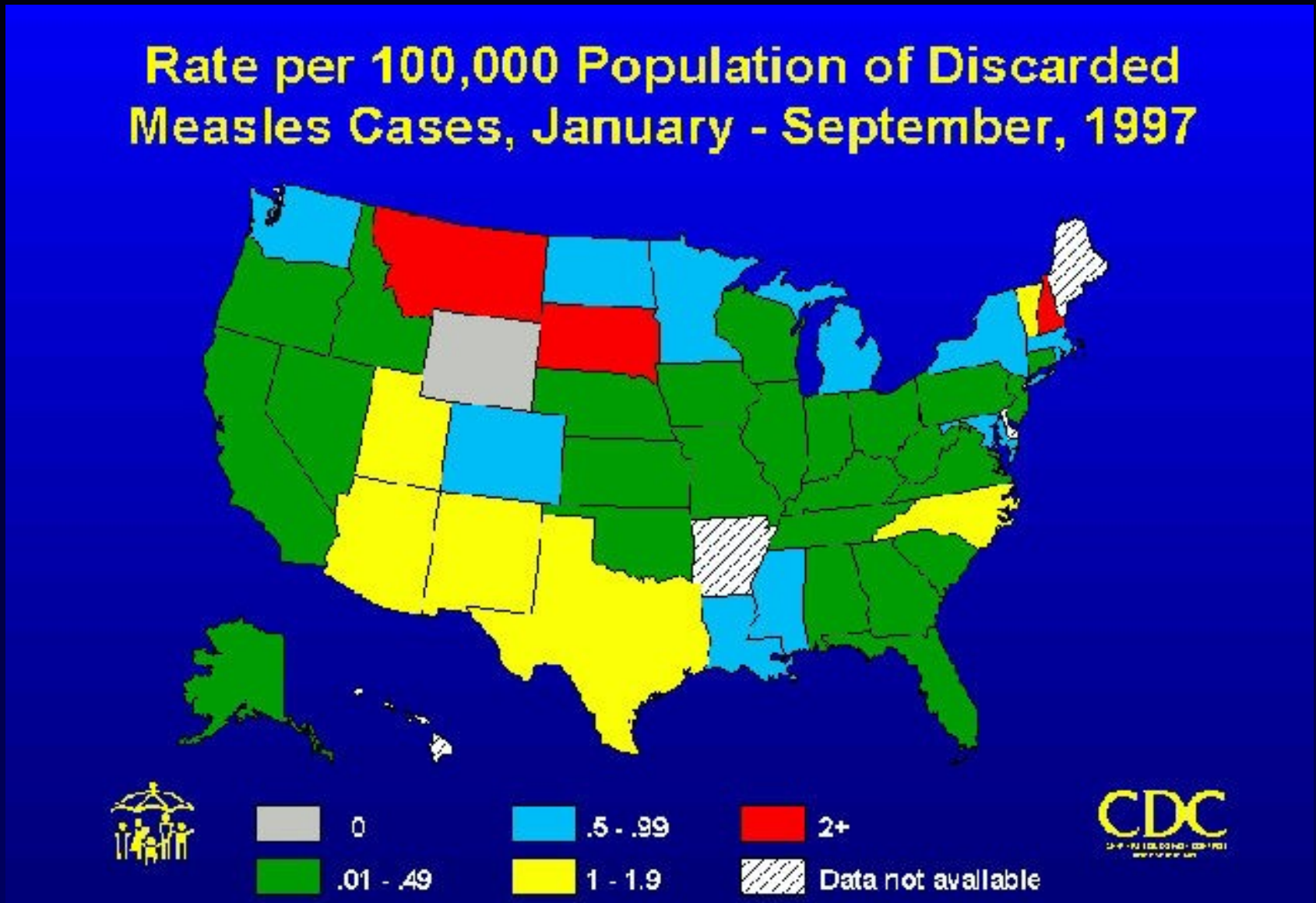
- Western Hemisphere and most of Europe
  - Vaccine strategies (2 shots) have interrupted transmission
- Middle East, Arabian Peninsula
  - Decreasing #’s with vaccination campaigns
- Africa
  - Poor control; most of the 800,000 deaths

Measles: Distribution

Reported Measles Cases
Region of the Americas, 1980 - 1998

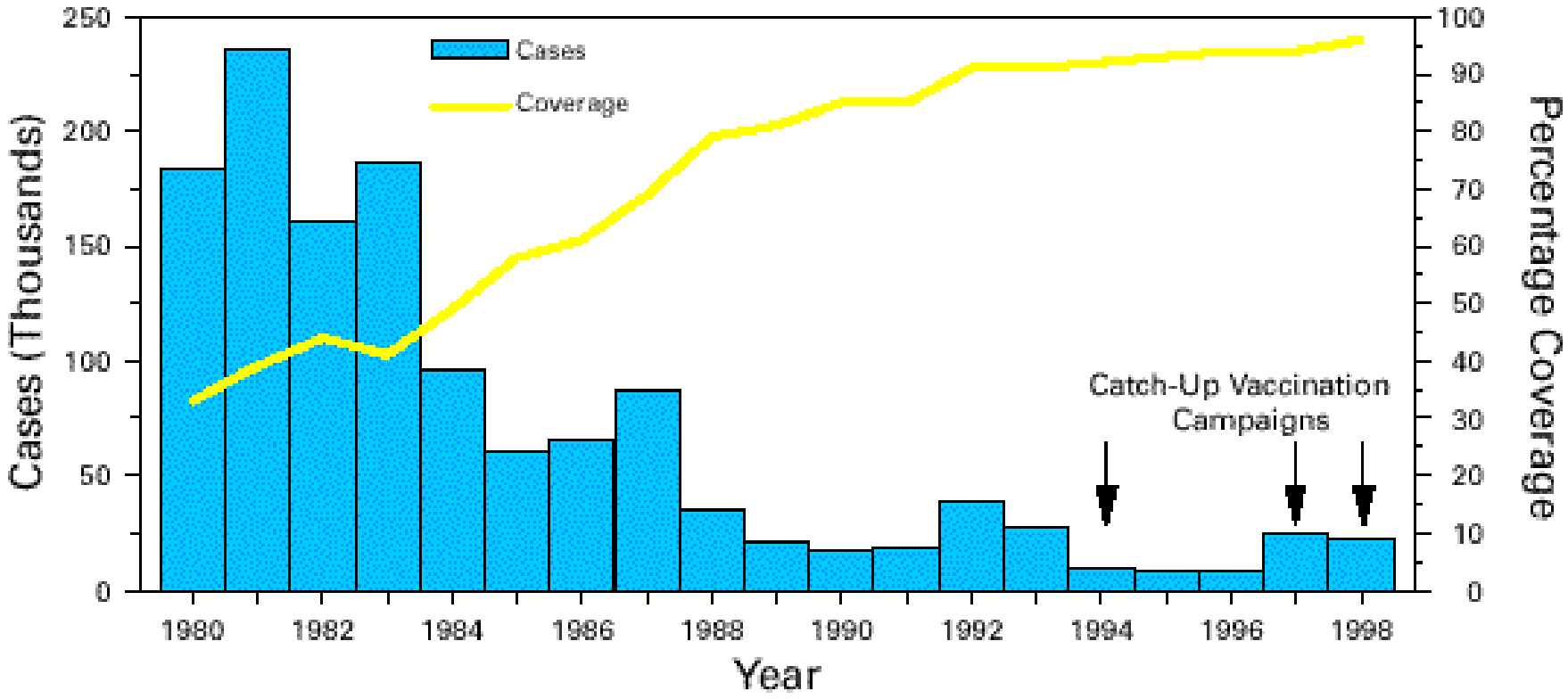


Measles: Distribution



Measles: Distribution

FIGURE 1. Reported number of measles cases and measles vaccination coverage, by year — World Health Organization, 14 countries,* Eastern Mediterranean Region, 1980–1998



*Bahrain, Cyprus, Iran, Jordan, Kuwait, Lebanon, Morocco, Oman, Palestine National Authority and Palestinian populations served by United Nations Relief and Works Agency, Qatar, Saudi Arabia, Syria, Tunisia, and United Arab Emirates.

Measles: Transmission

- Person to person transmission
  - Humans are only reservoir
  - Droplet nuclei or aerosols
- Highly contagious
  - 90% attack rate for close contacts
  - In MD office – transmitted 2 hours later
- Patients are contagious for 7-10 days
  - Begins with onset of symptoms
  - Includes 2-4 day prodrome before the rash

Measles: Pathophysiology

- Incubation: 10-12 days [8-16]
- Local reproduction in the pharyngeal lymphoid tissue
- Brief viremia on days 2-3
  - Spreads to other lymphoid tissues
  - Infects mono’s and macrophages
- Secondary viremia on days 7-10
  - Spreads throughout body
- Prodrome of 2-4 days
- Characteristic rash

Measles: Signs and Symptoms

- Prodrome
  - Cough
    - NP, worsens over 4 days, then improves
    - Lasts through entire illness (7-10 days)
  - Conjunctivitis (purulent), coryza
    - May include photophobia
    - Lasts 6-8 days
  - Fever: 38-40^{o} C: subsides after 1 week
  - Diarrhea
    - Chronic, serious if previously malnourished
    - State of prolonged virus shedding

Measles: Signs and Symptoms

- Koplik's spots
  - Part of prodrome: day 1-3 before rash
  - Raised papules on buccal mucosa and conjunctiva
  - Usually adjacent to molars
  - Often white on red base
  - Disappear about time rash occurs

Measles: Signs and Symptoms

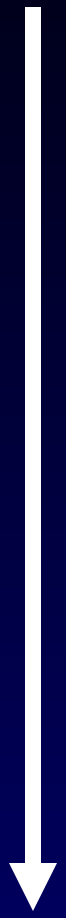
Rash

Hairline Behind Ears

Face

Trunk

Limbs



- Erythematous papular eruption
- Travels inferior over 2-3 days
- Coalesces into macular “splotches”
- Often desquamates at end of illness

Measles: Signs and Symptoms

- Peak of Illness
  - 2-4 days after onset of rash
- Other signs and symptoms
  - Anorexia, malaise, LAD, HSM
- Resolution
  - Rapid improvement at end of febrile period (1 week)
  - Complete recovery in 10-14 days
- Pearl: darker-skinned children
  - Sandpaper feel to rash may be helpful

Measles: Signs and Symptoms

- Atypical Measles
  - Occurs in those vaccinated in 1960's (killed vaccine)
  - Actually an immune response to wild-type measles
  - High fever, cough, abdominal pain, headache
  - Rash: extremities moving centrally
    - More petechia, vesicles, edema than typical dz
  - Elevated LFT's
  - "Nodular pneumonitis"
  - Should re-vaccinate these patients

Measles: Complications

- Acute Postinfectious Encephalitis
  - 1-4/1000 with 15% mortality
  - 2-6 days after rash
  - Mild to fulminant (death in 24 hours)
  - 25% morbidity (seizures, decreased fct)
- Secondary infections
- Subacute Sclerosing Panencephalitis–SSPE
  - 2-15 years after infection
  - Progressive behavioral changes

Measles: Complications

- Eating difficulties
  - Stomatitis
  - Cancrum oris (painful oral lesions)
- Laryngitis, laryngotracheitis
- Xeropthalmia and keratomalacia
- Diarrhea
- Myocarditis with EKG abnormalities
- Elevated LFT’s
- Fetal loss
- Pneumonia

Measles: Diagnosis / Clinical

- Clusters of children with fever, cough, conjunctivitis, coryza, morbilliform rash
- Koplik’s spots can be classic, but easily missed

Measles: Diagnosis / Lab

- IgM serum antibody after onset of rash
  - Only single test; no acute / convalescent
- UK: RIA for IgM in oral secretions
- Acute and Convalescent sera
  - EIA or HIA – need samples 4-6 wks apart
- Virus isolation
  - Can even compare virus genomes
  - Expensive and at reference labs
  - Only way to distinguish infection from vaccine

Measles: Differential Diagnosis

- Infectious
  - Scarlet fever
  - Rubella
  - Parvovirus B-19
  - Roseola
  - Enterovirus
  - Meningococcemia
  - Typhys
  - Tick Fever
  - Secondary syphilis
  - Mononucleosis
- Non-Infectious
  - Kawasaki's disease
  - Steven's Johnson syndrome
  - Drug reaction
    - Esp PCN drugs

Measles: Prognosis

- Mortality varies by age / nutritional status
  - Historically 1-5%
    - Higher with close contact secondary cases from presumed high viral exposure
  - US from ‘89-’91: mortality = 3/1000
  - West Africa/Asia: 25%
  - Death: pneumonia, malnutrition, diarrhea
- Risk factors
  - Immune compromise, Vitamin A deficiency
- Delayed excess mortality
  - Higher rates of death from other causes after measles infection in developing world

Measles: Treatment

- Supportive Care
  - Rest, hydration, nutrition, prn meds
  - Look for and treat bacterial super-infections
  - Rinse eyes daily (saline or sterile water)
- Vitamin A
  - May decrease mortality by 40%
  - Benefit may be independent of deficiency
  - WHO recs for both hospitalized and less ill
- Ribavirin
  - Inhibits viral replication in cell culture
  - Limited benefit in immune compromised patients
  - High cost makes = impractical in developing world

Measles: Treatment*

Vit-A → Age↓	Initial Dose	Final Dose 2 weeks later
0 – 5 Months	50,000 IU / day X 2 days	50,000 IU
6 – 11 Months	100,000 IU / day X 2 days	100,000 IU
>12 Months	200,000 IU / day X 2 days	200,000 IU

**WHO Recommendations*

Measles: Prevention

- Maternal antibodies
  - Protect for 3-12 months; usually 6 months
  - Presence of Ab's makes vaccine less effective
- Passive Immunization
  - Gamma globulin (0.25mg/kg)
  - For: high risk pts and exposure within 6 days
    - Pregnant, immune suppressed, children too young for vaccine, active TB, leukemia, known HIV
  - Impractical for developing world

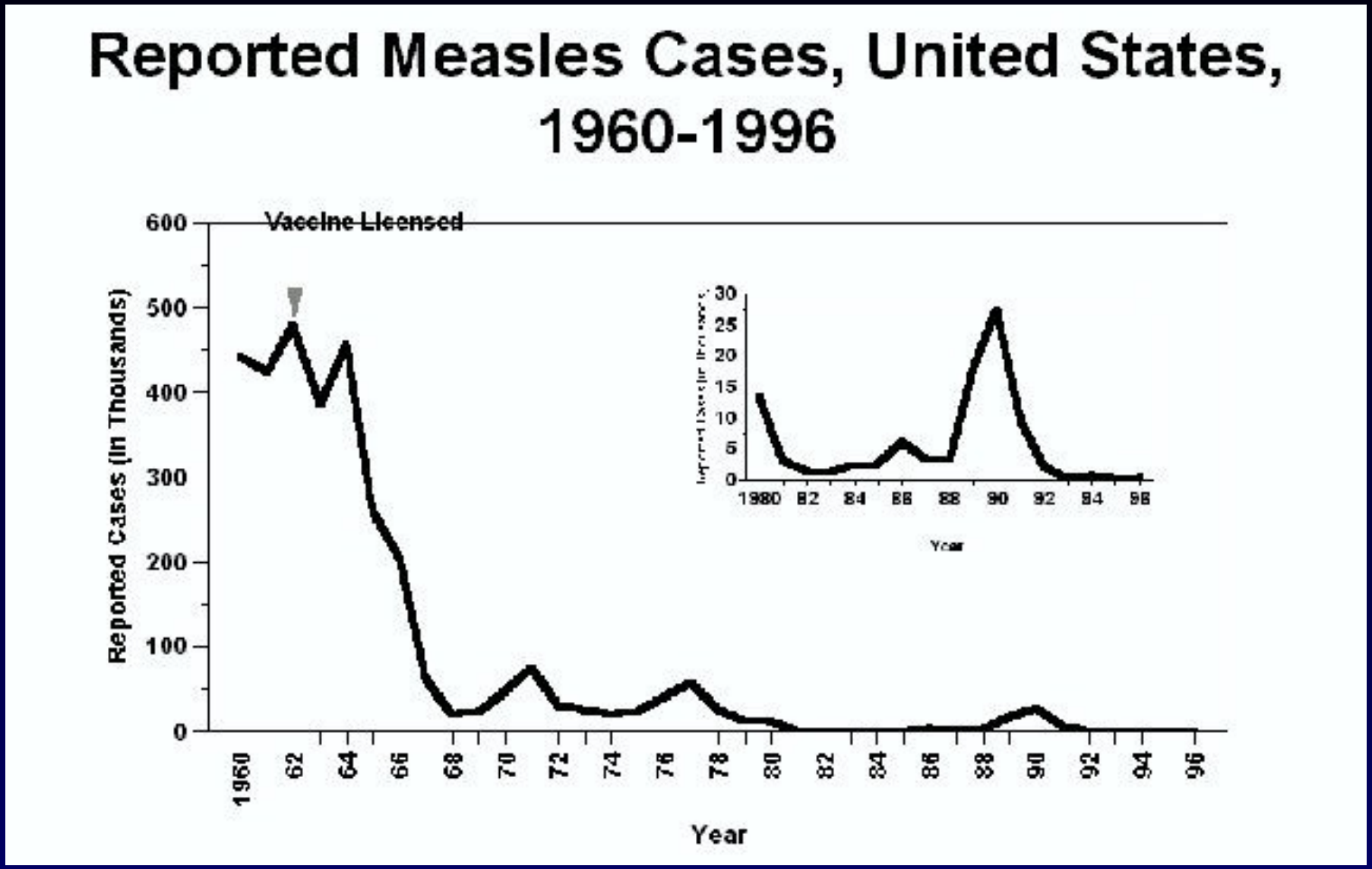
Measles: Prevention

- Vaccine Immunization
  - Live attenuated vaccine
  - Usually given with MMR
  - Efficacy (seroconversion)
    - 9 months: 80-85% (used in developing countries)
    - ≥15 months: 95% (used in developed world)
  - Contraindications (live vaccine)
    - Immune suppressed, leukemia, lymphoma, pregnancy, anaphylaxis to neomycin or gelatin
    - Most recommend vaccinating HIV patients

Measles: Prevention

- Vitamin A
  - Recommended at regular intervals (3-6 months) in developing countries
  - Targets children >= 6 months old
  - Decrease mortality by improving nutrition
  - Benefit likely involves many infections, but measles is at the top

Measles: Prevention



Measles: Mission Impact

- One of the first disease that can wreak havoc on displaced populations
  - War torn areas
  - Refugee camps
- Preventable
  - Vitamin A can be given immediately
  - One of first vaccinations to considere

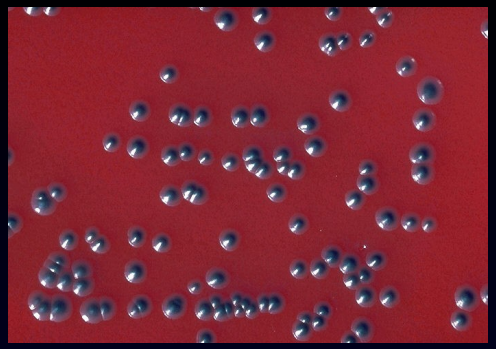
Measles: Summary

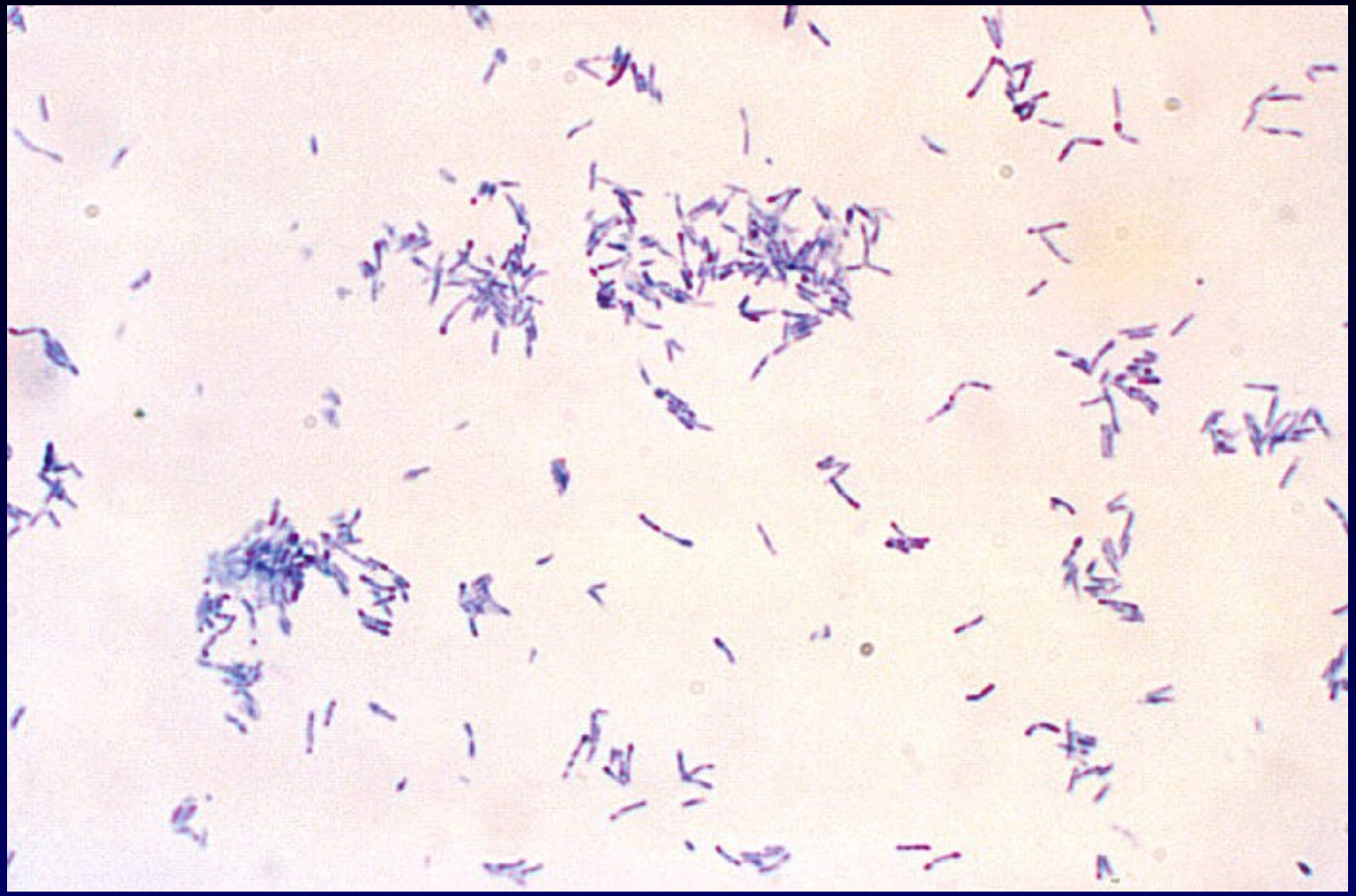
- Distribution: worldwide; worst in Africa
- Clinical Disease
  - Prodrome, Koplik's spots, morbilliform rash
- Treatment: supportive and Vitamin A
- Diagnosis: clinical, IgM serum antibody
- Prevention: Vitamin A, Vaccine
- Mission Impact:
  - Devastating disease of refugees
  - Priority when giving aide to displaced people

Diphtheria: Basic Characteristics

- Corynebacterium diphtheriae
  - Diphtherite (Greek) for hide or leather
- Pleomorphic gram + bacillus
- Curved or club-shaped
- 4 species
  - Mitis, gravis, intermedius, belfanti
  - C. ulcerans (bovine strain) can cause dz

Diphtheria





Diphtheria: Geographic Distribution

- Pre-vaccine
  - Highly endemic in temperate climates
  - One of leaders of childhood death
  - Affected elementary aged children
  - Fall peaks (? b/c of school)
  - Big epidemics every several years

Diphtheria: Geographic Distribution

- Post-Vaccine Era (1930's and '40's)
  - US, Canada, Western Europe
    - Almost eliminated
  - Resurgence in Germany/Europe in WW II
  - Today, some European countries haven't reported cases for 20 years
- Tropical Areas: not a big problem
  - Cutaneous infections hyperendemic

Diphtheria: Mode of Transmission

- Humans only known hosts
- Contagious
  - Respiratory tract droplets
  - Contact with lesions
  - Fomites: dust for up to 3-6 months
  - Respiratory and contact precautions
  - Incubation: 2-4 days but up to 7

Diphtheria: Pathogenesis

- Respiratory Diphtheria
  - Attaches: mucosal surface of nasopharynx
  - Toxin produced esp with low [Fe]
  - Blocks protein synthesis by interfering with elongation factor – 2
  - Affects local tissue as well as distal sites
- Cutaneous Diphtheria
  - New or super-infecting old wounds

Diphtheria: Signs and Symptoms

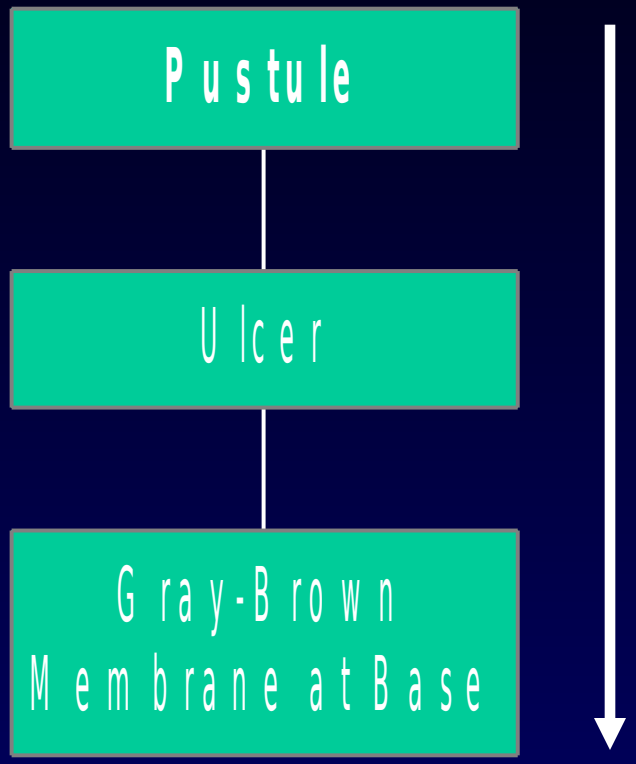
- Primary Infections
  - Respiratory Disease
  - Cutaneous Disease
- Secondary sites from toxin
  - Cardiac Disease
  - Neurological disease

Diphtheria: Signs and Symptoms

- Respiratory Diphtheria
  - Usually nasopharyngeal
  - Sore throat, malaise = most common
  - Characteristic membrane forms
    - Initially white and smooth → grey
    - Later patches of green and black = necrosis
    - Size dictates problems: can affect breathing
  - Cervical LAD and edema = bull neck

Diphtheria: Signs and Symptoms

- Cutaneous diphtheria
  - Superinfects old wounds
  - Can be primary infx
  - High levels of immunity to prevent systemic symptoms
  - Higher risk of transmission



Diphtheria: Signs and Symptoms

- Cardiac Disease
  - Myocarditis with significant dysfunction
  - Occurs in 10-20% of pts with resp dz
  - Severity correlates with respiratory dz
  - Mild: ST-segment and T-wave abnl
  - Severe: LBBB, AV block
  - Injury can be permanent if survived
  - Decrease incidence with tx within 4 days

Diphtheria: Signs and Symptoms

- Neurologic Disease
  - 10% pts with resp dz (range: 3-43%)
  - 75% of patients with severe disease
  - Severity correlates with respiratory dz
  - Cranial Nerves
    - IX, X early (10 d): dysphonia, liquid regurgitation
    - Other CN's occur 2-5 weeks after onset of illness
  - Peripheral Neuropathy (primarily motor)
    - Late: 3-12 weeks;
    - Can occur in absence of CN deficits

Diphtheria: Complications

- Airway Obstruction
  - Extension of membrane into larynx
  - 4-15% of respiratory cases
  - Fatal in 40-100%
  - Prevent: early intubation
- Pneumonia: 2-7%
  - Rarely from diphtheria
  - Aspiration, post-obstruction

Diphtheria Diagnosis: Clinical

- Pharyngeal disease with cardiac +/- neurological abnormalities
- Pseudomembrane
  - Rubs off easily, but bleeds underneath
- Few causes of “bull neck”
  - Ludwig’s angina
  - Subcutaneous air

Diphtheria Diagnosis: Laboratory

- Culture on selective media
  - Tellurite media (Tinsdale), blood agar, Loffler slant incubated at 35-37 degrees
  - Gram stain can be helpful early
  - Sample sources
    - Nasal and pharyngeal swabs
      - Membrane itself or underneath
    - Deep samples from skin (not surface swabs)
- Toxin Production
  - Multiple approaches

Diphtheria: Treatment

- Hospitalize all patients if possible
- Contact and droplet precautions
  - Maintain until 2 negative cultures
- Antitoxin
  - Most effective the earlier given
    - Not effective if given after 4 days of illness
  - Equine hyper-immune serum
    - Scratch test on forearm with 1:100 dilution
- Antibiotics
  - 2 week course

Diphtheria: Treatment

- Antitoxin
  - Available from CDC (404) 639-8200
  - Pharyx / Larynx: 20K-40K U IV
  - Nasopharynx: 40-60K U IV
  - Extensive dz or sx > 3d: 80K-120K U IV
- Erythromycin
  - 40-50mg/kg/d (max 2g/d) divided in 4 doses
  - Alternate = PCN
    - Pen G 100K-150K U/kg/d divided q6H (max 12-20 mil)
    - Procaine PCN 25K-50K U/kg/d divided q12 (max 1.2 mil)

Diphtheria: Treatment

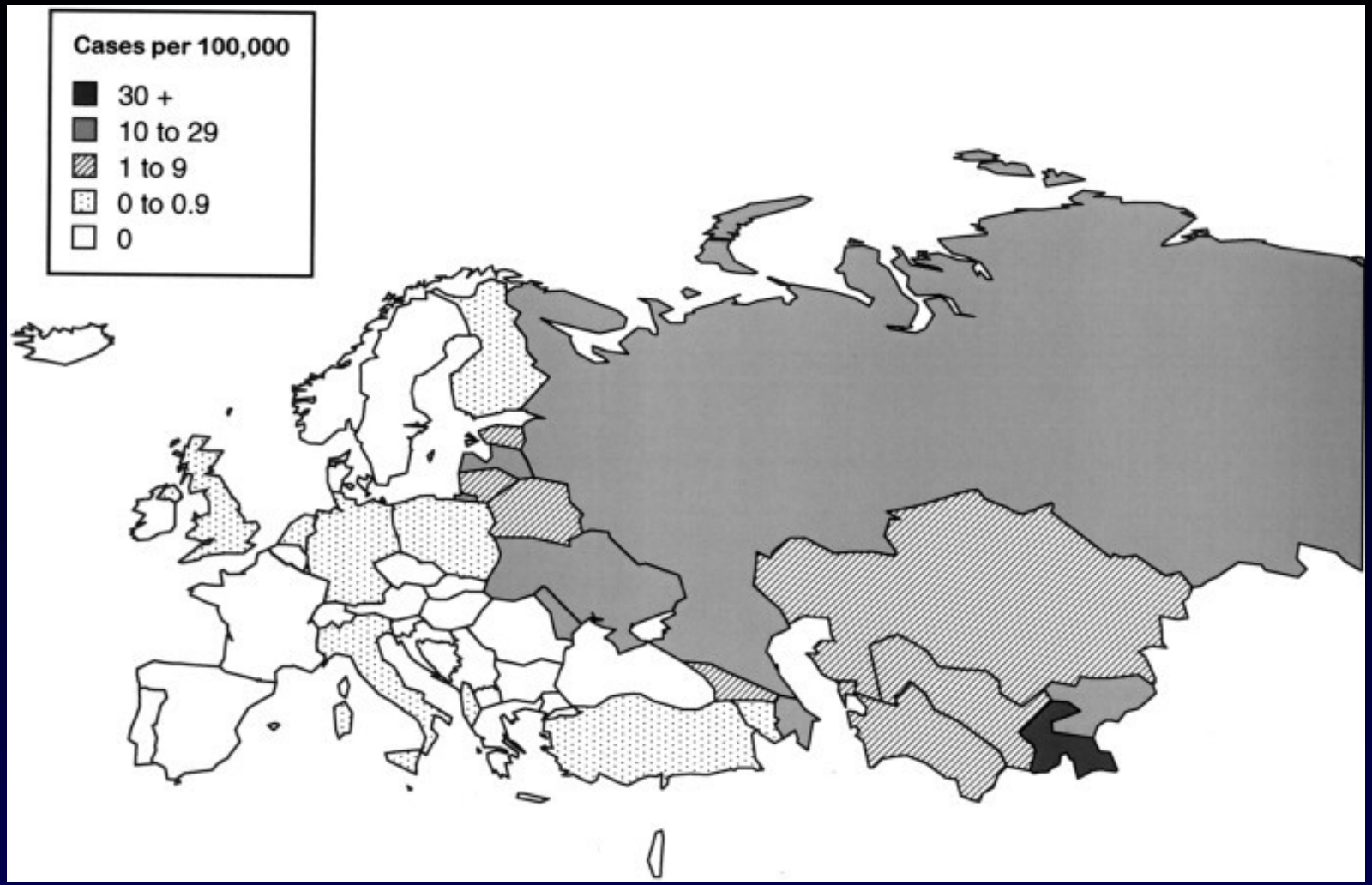
- Managing Outbreak
  - Notify local health officials
  - Close contact tracing
    - Observe for 1 week; culture for carriage
  - Prophylaxis of close contacts
    - Oral emycin (same as IV dose) X 1 week
    - Single IM benzathine Pen G
      - 600K U if <30 kg; 1.2 mil U if >30 kg

Diphtheria: Prevention

- Vaccine Preventable Disease
- Toxoid Vaccine
  - Full strength=D (DTaP); 1/5 strength=d (Td)
  - US Schedule
    - 3 IM injections 4-8 wk intervals; 4th 6-12 mo later
    - > 7yo: 2 X IM at 4-8 wk intervals; 3rd 6-12 mo later
  - Booster
    - DTaP at school entry if started at <4 weeks old
    - Adults: every 10 years (d)
- Global diphtheria decreased by 70% from mid 1970's to early 1990's.

Diphtheria: Mission Impact

- Epidemic outbreak in former Soviet Union shows what happens when prevention measures are lifted and a vulnerable population is at risk.



Reported diphtheria incidence per 100,000 population in the European Region, World Health Organization, 1995

Diphtheria: Mission Impact

- Former Soviet Union
  - Peak = 50,412 cases (39,582 in Rus Fed)
  - Rus Fed 1993: 2/3 of cases > 14 y.o.
  - Persons 40-49 y.o
    - 45% of all deaths = highest rate (1.3/100K)

Vitek CR and Wharton M. Diphtheria in the former Soviet Union: reemergence of a pandemic disease. EID 1993; 4(4):539-50.

Diphtheria: Mission Impact

- Former Soviet Union: What Went Wrong?
  - Susceptible adult population
  - Susceptible population of children
  - New clone introduced into area
  - Crowding in urban areas
  - Disruption in vaccine supply after break-up
  - Breakdown in public health systems

Diphtheria: Mission Impact

- Lessons learned
  - Vaccination effort controlled epidemic
  - National (Russian Federation) and International (for Independent States) came together to battle epidemic
  - Archetype for increased susceptibility in adults to childhood diseases with successful childhood vaccine campaigns?

Diphtheria: Summary

- Distribution: sporadic cases but recent outbreak in former Soviet Union and Independent States
- Clinical Disease
  - Nasopharyngeal: pseudomembrane, bull neck
- Treatment: Antitoxin + Abx (Emycin > PCN)
- Diagnosis: Clinical, Culture and show toxin
- Prevention: Vaccination, Abx (Emycin, PCN)
- Mission Impact:
  - Devastating disease in susceptible population
  - Vaccination + abx aborted recent epidemic

Meningococcemia: Basic Characteristics

- Neisseria meningitidis
- Aerobic gram-negative diplococcus
- Serogroups based on polysaccharide capsule of cell wall
  - A, B, C, Y, and W-135 most common
  - Each serogroup has multiple serotypes

Meningococcemia: Basic Characteristics

Photo: UT Houston Medical School Website

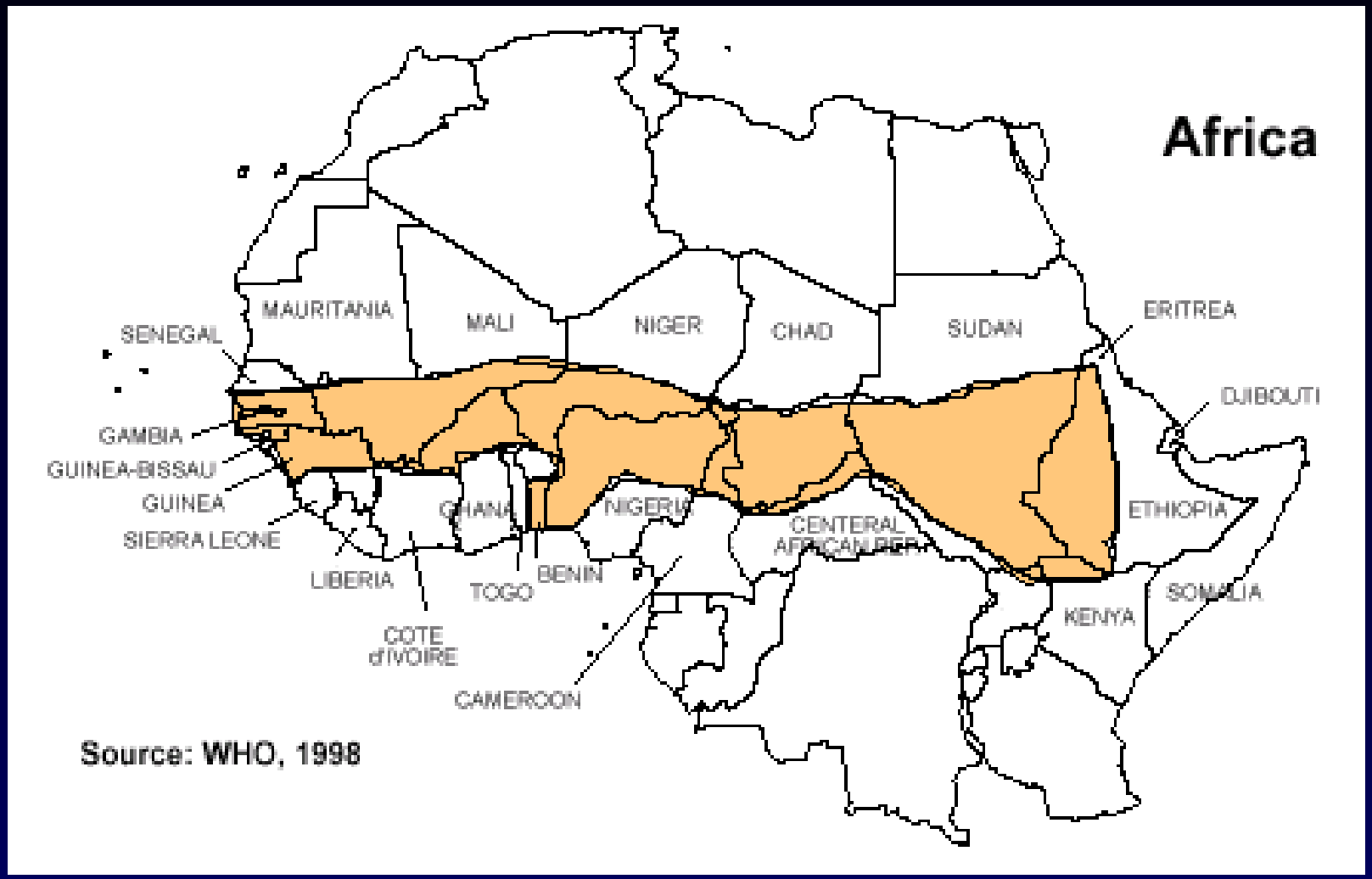
Meningococcemia: Basic Characteristics

- Humans are only reservoir
- Fulminant disease
- High mortality – not improved for 50 yrs
- Targets adolescents

Meningococcus: Geographic Distribution

- Industrialized nations
  - Localized outbreaks causing high alarm
  - 50% B group (endemic), 20% C (epidemic)
  - 1-2 per 100,000 per year
- Sub-Saharan Africa = “meningitis belt”
  - Baseline rate = 10-25 per 100,000 per year
  - Group A (some C) strains cause epidemics every 8-12 years

Map: Areas with Frequent Epidemics of Meningococcal Meningitis, 2000



Health Information for International Travel, 2001–2002, CDC

Meningococcus: Mode of Transmission

- Respiratory droplets from carriers
- Carrier rates
  - 95% in group A epidemics
  - 50% in military recruits
  - 10-15% general US population
  - Rates increase with crowding (prison, refugees, college dorms)
- Highest attack rates in Winter and Spring

Ferguson et al. N. meningitidis: presentation, treatment, and prevention. J pediatr Health Care 2002; 16:119-24

Meningococcus: Pathophysiology

- 1. Adhere
  - After protease inactivation of secretory IgA
  - Attach to non-ciliated pharyngeal mucosa
- 2. Colonization
  - Nasopharynx and UR tract
- 3. Invasion
- Facilitators: other infections, passive or active smoke, s/p tonsillectomy

Meningococcus: Signs and Symptoms

- Acute bacterial meningitis
  - Headache, nausea, vomiting, meningismus
- Rapidly progressive
- Pharyngitis usually precedes meningitis
- Chills, malaise common
- High fever is norm – no fever is poor prognostic sign

Meningococcus: Signs and Symptoms

- Petechial rash
  - Starts distally and spreads to trunk
  - Palms and soles involved commonly
  - develops over hours to days

Meningococcus: Signs and Symptoms

- Waterhouse-Friederichsen syndrome
  - Fulminant meningococcemia
  - Vascular collapse develops over hours
  - Occurs in 5-15% of meningitis cases
  - Preceded by restlessness, MS changes
- Acute meningococcemia
  - Presents as gram negative sepsis
- Chronic meningitis
  - Uncommon more indolent disease

Meningococcus: M and m

- Pneumonia
  - 15-20% of cases
  - May occur alone
- DIC
- Adrenal hemorrhage
- Distal necrosis / gangrene
- Mortality
  - 7-70%
  - Varies by SES
  - Cause: circularory collapse
  - Occurs early in disease

Meningococcus Diagnosis: Clinical

- Fulminant bacterial meningitis
- Charcteristic petechial rash
  - Extremities to trunk

Meningococcus Diagnosis: Laboratory

- Culture organism
  - CSF, blood, throat swab, skin lesions
  - Much higher yield if pre-abx
    - Blood Cx + 50% pre vs 5% post
  - Skin lesions GS + in 70%
- CSF: classic for bacterial meningitis
  - PMN predominance, low glucose, normal to high protein
  - Gram stain + in 70%
- Fastidious: plated on chocolate agar ASAP

Meningococcus: Differential Diagnosis

- Rickettsial diseases
- Toxic shock syndrome
- Vasculitis
- Viral illness

Meningococcus: Treatment

	Adults	Children
1st Choice	Pen G 2.4 mil U IV Divided q2-4 H	Pen G 0.25 mil U/kg/d IV Divided q2-4 H
Alternative	Ceftriaxone 2g IV q12 Chlor 50-100mg/kg/d IV or PO q6H	Ceft 80-100mg/kg/d IV q12 Chlor - same as adults

Treat for 4-10 days

Wilson. Current diagnosis and treatment in infectious diseases. 2001. pp546

Meningococcus: Prevention

- Vaccine
  - Quadrivalent (A, C, Y, W-135)
  - 0.5 ml SC X 1 (repeat if < 4 y.o)
- Prophylaxis of contacts
  - Rifampin 10mg/kg (max 600mg) po q12 X 4 doses
  - Cipro 500 or 750mg po X 1 dose
  - Ceftriaxone 250mg IM X 1 (125 for kids)
- Respiratory isolation until 24H on tx

Meningococcus: Mission Impact

- Sporadic cases and outbreaks can occur throughout the world
- Consider in missions with proximity to large numbers of children
- High risk in sub-Saharan Africa
- Vaccine preventable disease

Meningococcus: Summary

- Distribution: epidemics in sub-Saharan Africa
- Clinical Disease
  - Fulminant meningitis, shock, DIC, petechial rash
- Treatment: PCN > Ceftriaxone > Chloramphen
- Diagnosis: Clinical, Culture in lab
- Prevention: Vaccine, Abx (Rifampin, Cipro, Ctx)
- Mission Impact:
  - Devastating disease even if few cases
  - Vaccine and abx can abort outbreaks

Suggested Reading

- Barnett et al. Seroprevalence of measles, rubella, and varicella in refugees. CID 2002; 35:403-8.
- MMR – Vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps. MMWR 1998; 47(RR-8):
- Redd SC, Breman JG. *Measles*. Hunter's tropical medicine and emerging infectious diseases, 8th ed. 2000; WB Saunders 199-206
- Sommer A. Vitamin A prophylaxis. Archives of disease in childhood. 1997; 77(3): 191-4.
- Stalkup JR. A review of measles virus. Dermatology Clinics 2002: 209-15.

Suggested Reading

- Diphtheria, tetanus, and pertussis: recommendations for vaccine use and other preventive measures. MMWR 1991; 40(RR10):1-28.
- Galazka A. The changing epidemiology of diphtheria in the vaccine era. JID 2000; 181(Suppl 1):S2-9.
- Hadfield et al. The pathology of diphtheria. JID 2000; 181(Suppl 1):S116-20
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Suggested Reading

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